EMBO reports

Everything flows

A process perspective on life

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Sometimes, an important aspect of the world is so obvious that we simply take it for granted. We rarely discuss it or even think about it explicitly. In our opinion, the processual nature of reality—that it is fundamentally a sequence of interconnected occurrences or events—is one such aspect: we continually experience change, but tend instead to explain the world in terms of static things. For historical reasons, Western philosophy—and with it the scientific world view—largely adheres to this notion: that substance is fundamental and processes are mere epiphenomena or derived properties of things. The tradition can be traced back to ancient Greek philosophers, such as the atomists, and it is still prominent today in both research and everyday life. Almost without exception, science seeks explanations in terms of things that exhibit some kind of agency: the fundamental particles of physics, for instance, or genes as hereditary factors and determinants of form, physiology and behaviour in biology.

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As substance- and process-based views provide two complementary ways to explain reality, we think that the focus on substance has become unnecessarily limiting and is now impeding conceptual advances in science. The process perspective provides a richer and more natural picture of reality for three main reasons. First, it is difficult to find anything that is truly universally and eternally unchangeable. Everything changes—galaxies, stars, planets, landscapes, ecosystems, organisms, cells, genetic sequences, molecules and even atoms—although at vastly different timescales. Second, substance does not have any effect without process. If something does not dynamically interact with any other thing, it is inert and hence irrelevant. In fact, it cannot even be perceived, since perception is itself a dynamic interaction. Finally, while nothing is perceivable without process, there are many processes that are not things: a thunderstorm, for example, or a burning flame, or a disease running through a population, or a story being told, or your thoughts while reading this paper, or the headache some of us get when thinking about metaphysics. It is true that these phenomena involve entities—molecules, viral particles or electrochemical potentials in our nerve cells—but these entities are exchangeable; they come and go during the lifetime of a process. What defines and characterises a process are the dynamical interactions among constituents, not the constituents *per se* (see Fig 1).

While this has been recognised for a while now in physics—a discipline rich in processual concepts such as fields and forces—it has been somewhat neglected in biology (see Sidebar A for discussion). As mentioned at the outset, this may simply be because the processual nature of reality seems too trivial to merit any discussion. Indeed, the authors' own disciplines of evolutionary, developmental and systems biology obviously deal with dynamic processes. But surprisingly, even in these fields, we often attempt to explain phenomena in terms of static entities.

One example is the identification of genes "for" some phenotype. Genes are often used as causal explanations for all sorts of physical traits, diseases and even behaviours. How they actually exert their agency is not clear and is far too often considered of secondary importance and hence not investigated properly. In this age of systems biology, it is still exceptional to find a study that rigorously assays gene expression dynamics. Ernst Mayr, among others, criticised the trend towards static explanations in evolutionary biology and dismissed population genetics, which focuses exclusively on the segregation of particulate hereditary factors, as "beanbag genetics". In systems biology, we are overwhelmed nowadays with "hairball graphs" of static networks that are supposed to explain a variety of complex biological processes without considering the dynamics of network interactions. Sadly, we simply seem to be repeating the conceptual shortcomings and mistakes of classical genetics at the higher level of systems and networks.

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In our view, the identification of genes and their interactions is not an end in itself—not a satisfactory explanation on its own—but only a starting point for investigating the *processes* that are implemented by regulatory networks. We believe that it is high time to move beyond hairballs.

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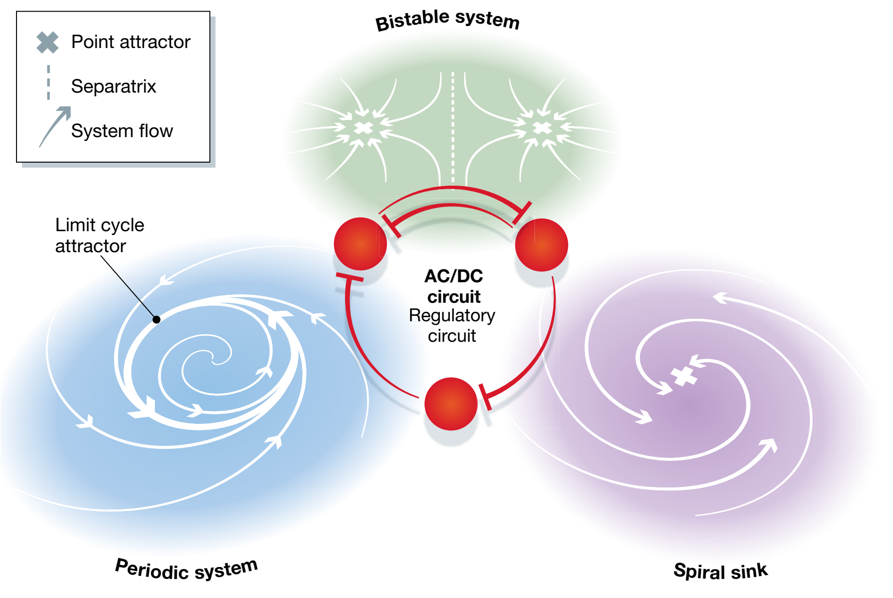

Figure 1. The topology of an AC/DC circuit.
The AC/DC circuit is so called because it is a minimal motif able to create both bistable (switch) and oscillatory behaviour. The figure illustrates that even a simple motif like the AC/DC circuit is able to produce very different dynamical behaviours (indicated by phase portraits in the background). Arrows represent the flow of the system (determining how state changes over time). Crosses indicate point attractors; the phase portrait on top shows a bistable system with two attractors and a separatrix between the corresponding two basins of attraction (indicated by dashed line); on the right, we show a spiral sink, a particular type of point attractor that leads to damped (temporary) oscillations before the system state becomes fixed; the lower left depicts a periodic system: its bold line depicts a limit cycle attractor producing stable oscillations.

Investigations of the dynamics of biological systems could draw on a rich tradition of process thinking in philosophy and science, going back to Heraclitus, Aristotle, Leibniz, Bergson, the American Pragmatists—Pierce, Dewey, James—and Alfred North Whitehead, among others. Many experimental and theoretical biologists have made important contributions focussing explicitly on processes (see Sidebar A for examples). Examples from developmental and evolutionary biology include Conrad Hal Waddington with his epigenetic landscape, which was put on mathematically rigorous foundations by René Thom. Stuart Kauffman used concepts from dynamical systems theory to study emergent order in complex evolving networks and to propose an exploratory evolutionary dynamics forever progressing into the next "adjacent possible"—a state never before reached by the evolving system. Brian Goodwin developed a structuralist theory of evolution and development based on morphogenetic fields. Similar views were put forward around the same time by Pere Alberch and George Oster. All these cases emphasise the principles that govern the dynamics of development and evolution; the biochemical nature of the genes involved is of less importance than the way they interact with each other.

But what exactly is this process perspective we are talking about? How does it differ from the traditional thing-oriented view? The most important question we need to tackle is what we mean by the statement: "the universe consists of fundamental processes, not things" (see Ladyman & Ross in Sidebar A). If processes are the basic building blocks of the world, surely they are actually things after all? And what are processes made of? One possible definition is that "[a] process is a coordinated group of changes in the complexion of reality, an organized family of occurrences that are systematically linked to one another either causally or functionally" (see Rescher in Sidebar A). In other words, processes consist of "occurrences", "events", "activities", none of which are things themselves: they do not exist outside the context of their process, and they are neither static nor inert. A good example of such a process is the flow of your consciousness as you are reading these words.

Having defined what a process is, it is important to point out three important differences between processes and things. First, processes are always interconnected, while static entities need not be. This leads to a world view emphasising relatedness and wholeness, in contrast to the reductionist stance, which seeks explanations by separating the individual constituents of a system. While a process view naturally accommodates agency, novelty or free will, rigorous interpretations of the traditional substance-based stance struggle to explain—or even deny—these kinds of phenomena.

The second difference concerns spatial and temporal extent. Boundaries must be well defined for identifying things, which are by definition discrete. This is not necessarily the case for processes: the physical constituents of a process may come and go, and they can be transformed into something else over time. It is often impossible to define the exact spatial limits or duration of a process. Becoming is more important than being. Everything flows, as Heraclitus stated with his *panta rhei*.

Lastly, the lack of discreteness of processes implies that the world is, at its heart, continuous. This in turn means that the universe could possibly contain an infinity of different processes, an infinity of occurrences and, hence, an infinity of possible experiences.

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It should be evident by now that processes are harder to define and delimit than things. However, if we consider processes as a fundamental aspect of reality, there must be a way to unambiguously identify and characterise them. Since it is impossible to delimit exact spatial and temporal boundaries, we need to consider internal continuity and connectedness of a system. Processes of the same kind share a common structure based on rules that determine how one occurrence follows from another and create change. This renders specific types of processes recognisable and reproducible.

What do these considerations mean for biology? And what kind of practical advantages do these theoretical ideas offer to biologists who work on specific systems and problems in the laboratory? Over the past few decades, we have seen a slow but widespread and persistent shift of focus from identifying the constituents of living beings and processes, to studying the dynamical interactions between them. These interactions are essential for understanding most biological phenomena. And yet, while some disciplines have adopted a process perspective quickly and early on, such as physiology, others have been a bit slower in realising its importance.

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An interesting example to consider is evolutionary biology. On the one hand, its conceptual framework is explicitly built on the study of population *dynamics*, the change of allele frequencies over time. On the other hand, it still largely ignores the processual and open nature of the genotype-to-phenotype relation, which is crucial for explaining the active role of the environment in development and evolution, and the varying abilities of different groups of organisms to adapt to changing environmental conditions. From our perspective, it is obvious that evolutionary and developmental dynamics represent complementary aspects of one and the same overarching process, and it is the exclusion of one of these aspects, not its inclusion, that needs justification (see Sidebar A).

Other examples that illustrate the importance of process thinking in biology come from disciplines across the board and across all scales. It is increasingly appreciated that protein configurations and modifications, and the complexes proteins are part of, constantly change over time. Since such dynamic changes are essential for the function of many molecular machines, static protein structures are not sufficient to explain metabolic and regulatory functions of the cell. Moving one level up, cell and developmental biologists are now able to characterise the dynamics of intracellular and tissue-level molecular processes in great detail, down to individual molecules, thanks to spectacular recent advances in live imaging technology. Movies of such processes are among the visually most striking results

Sidebar A: Further Reading

The processual nature of reality

The process perspective holds that reality is fundamentally dynamic: the basic constituents of the universe are interconnected sequences of occurrences or events. Accordingly, reality must be described and explained using explicitly dynamic, that is processual, concepts rather than notions representing static "things" or entities. For more, see: Rescher N (1996) *Process Metaphysics – An Introduction to Process Philosophy*. Albany, NY: State University of New York Press; Ladyman J, Ross D (2007) *Every Thing Must Go – Metaphysics Naturalized*. Oxford, UK: Oxford University Press.

Examples of processual concepts and approaches in biology

Waddington's "epigenetic landscape" is a classic processual concept. Introduced in 1957, it has experienced a recent resurgence among cell, developmental and evolutionary biologists. The epigenetic landscape describes the path to differentiation of a cell, tissue or developing system—in terms of a ball rolling down branching valleys of an undulating surface—and how this path reacts to external signals during development or genetic changes during evolution: Waddingotn CH (1957) *The Strategy of the Genes*. London, UK: George Allen & Unwin.

Waddington's landscape metaphor was translated into the mathematically rigorous conceptual framework of dynamical systems theory by René Thom, who treats morphogenesis in terms of structurally stable (i.e. robust) types of bifurcation events: Thom R (1976) *Structural Stability and Morphogenesis*. Reading MA, USA: W. A. Benjamin.

Our own work connects Waddington's landscape with contemporary notions of network evolution and provides specific empirical examples for the application of dynamical systems theory to the evolution of development. See, for example: Jaeger J, Monk N (2014) Bioattractors: dynamical systems theory and the evolution of regulatory processes. *The Journal of Physiology* 592: 2267–2281.

Developmental systems theory (DST) is an alternative philosophical approach, which considers development and evolution as a unified, intertwined process. An accessible introduction is given in Robert JS (2004) *Embryology, Epigenesis, and Evolution: Taking Development Seriously*. Cambridge, UK: Cambridge University Press.

Another interesting process philosophical perspective on biology is given by John Dupré, who goes beyond the perspectivism presented here (see also below) by interpreting the incompatibility of different levels of scientific explanations as evidence for the fundamental disunity of reality: Dupré J (2012) *Processes of Life – Essays in the Philosophy of Biology*. Oxford, UK: Oxford University Press.

Stuart Kauffman's work on exploratory evolutionary dynamics

Kauffman's pioneering work uses computer simulations to investigate the dynamics of complex regulatory networks. In his "Investigations", he develops the idea that evolving biological systems are continuously exploring the "adjacent possible" (network states and phenotypes never realised before) resulting in a ceaselessly creative and innovative evolutionary process: Kauffman SA (1993) *The Origins of Order: Self Organization and Selection in Evolution*. Oxford, UK: Oxford University Press; Kauffman SA (1996) *At Home in the Universe: the Search for Laws of Self-Organization and Complexity*. Oxford, UK: Oxford University Press; Kauffman SA (2001) *Investigations*. Oxford, UK: Oxford University Press.

Biological structuralism (Brian Goodwin and others)

Adaptive evolutionary change requires natural selection on variable phenotypes. Structuralism focuses on the origin and non-random distribution of variability in organismic form by examining the regulatory principles that govern biological generative processes (e.g. development). It uses dynamical systems theory to provide a process-based organismic context in which genes can exert their effects: Oster G, Alberch P (1982) Evolution and bifurcation of developmental programs. *Evolution* 36: 444–459; Goodwin BC (1982) Development and evolution. *The Journal of Theoretical Biology* 97: 43–55; Goodwin BC (1990) Structuralism in biology. *Science Progress* 74: 227–244; Goodwin B (1994) *How The Leopard Changed Its Spots*. London, UK: Weidenfeld & Nicolson; Webster G, Goodwin BC (1996) *Form and Transformation: Generative and Relational Principles in Biology*. Cambridge, UK: Cambridge University Press.

Scientific perspectivism

Process philosophy provides a perspective on biology, which complements rather than replaces other forms of explanation. Scientific perspectivism argues that such explanatory pluralism is desirable, or indeed unavoidable, due to the subjective motivations, backgrounds and questions of different scientists and research communities at any given time. For a very concise and accessible introduction, see: Giere RN (2006) *Scientific Perspectivism*. Chicago IL, USA: The University of Chicago Press.

created by modern biology. However, it is important to keep in mind that they only provide descriptions—not explanations—of the phenomenally complex and orchestrated dynamic organisation of cells and developing organisms.

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Perhaps the best illustration of the importance of process thinking—as well as the limitations of the substance-based view—comes from the field of systems biology. Genetics and genomics try to identify the components and interactions that constitute complex biological systems. These days, high-throughput methods are producing hairball graphs at an unprecedented pace, but such depictions fall short of providing causal explanations. We know that identical regulatory network structures can implement all kinds of different behaviour. Studying the dynamics of these networks rather than the individual components is therefore essential for our understanding of complex regulatory phenomena. In fact, we believe that this constitutes *the* central challenge for modern systems biology. We must adopt process philosophy as the appropriate conceptual framework to realise the true potential of the systems biology approach.

> *"Science is a process, a constant interaction between the scientist, the question, and the structure of reality"*

Neurobiology and the cognitive sciences are those disciplines of biology that have embraced the process perspective most emphatically. It is impossible to think about the nerve impulses that provide the substrate for thought, and ultimately the higher-level phenomena of mind and consciousness, in any other than dynamic terms. This leads directly to the context in which a process perspective imposes itself most forcefully: the notion of the self, and its role in scientific inquiry. David Hume famously noted upon thorough introspection that there was no such thing as the "self", only ever-changing thoughts. What he did not realise in his puzzlement was that the self is not an unchanging static entity. We are not the same person we were a few years, or even months ago, but our identity is the continuity and unity of our thoughts and activities. We literally are what we do, an insight that has been at the foundation of Eastern philosophy for millennia.

Finally, process philosophy allows us to better understand the nature of science itself. Most scientists subscribe to a realist view of the world. We assume that there is a unique structure of reality that is at least partially accessible by rational means, the scientific method in particular. However, scientific inquiry always involves a subjective element: the scientist as an active agent. Somebody is coming up with questions and is implementing the theories and experiments required to answer them. Science is a process, a constant interaction between the scientist, the question and the structure of reality. In this sense, our knowledge, even scientific laws, are always context dependent, and only valid in relation to the subjective question we had, and the kind of explanation that we find satisfying. Each one of us brings his or her own perspective into the game. Ours, as we have explained in this essay, is a perspective based on process.

Conflict of interest

The authors declare that they have no conflict of interest.